

NIOSOME AS AN INNOVATIVE DRUG DELIVERY SYSTEM

Dhanvir Kaur¹, Sandeep Kumar²

EMAIL: dhanvir33215@gmail.com

Received 22nd January 2020,

Accepted 10th February 2020,

Online 5th March 2020

^{1,2}Department of Pharmaceutics,
ASBASJS College of Pharmacy, Bela
(Ropar), Punjab, India

ABSTRACT: Drug targeting is a kind of phenomenon in which drug gets distributed in the body in such a manner that the drug interacts with the target tissue at a cellular or subcellular level to achieve a desired therapeutic response at a desired site without undesirable interactions at other sites. This can be achieved by modern methods of targeting the drug delivery system such as niosome (vesicular system). Designing of the drug in the vesicular system has brought a new life to the old pre-existing drugs and thus has improved their therapeutic efficacies by controlling and sustaining the actions. Different novel approaches used for delivering these drugs include liposomes, microspheres, nanotechnology, micro emulsions, antibody-loaded drug delivery, magnetic microcapsules, implantable pumps and niosomes. Niosomes and liposomes are equiactive in drug delivery potential and both increase drug efficacy as compared with that of free drug. Niosomes are preferred over liposomes because the former exhibit high chemical stability and economy. Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic non-ionic surfactants, with or without incorporation of cholesterol or their lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Niosomes are promising vehicle for drug delivery and being non-ionic; and Niosomes are biodegradable, biocompatible non-immunogenic and exhibit flexibility in their structural characterization. Niosomes have been widely evaluated for controlled release and targeted delivery for the treatment of cancer, viral infections and other microbial diseases. Niosomes can entrap both hydrophilic and lipophilic drugs and can prolong the circulation of the entrapped drug in body. Encapsulation of drug in vesicular system can be predicted to prolong the existence of drug in the systemic circulation and enhance penetration into target tissue, perhaps reduce toxicity if selective uptake can be achieved.

KEYWORDS: Niosome, Cholesterol, Hydrophilic and Lipophilic drugs, Surfactant, Targeted delivery, Bioavailability Improvement, Factors, Applications, Therapeutic efficacy.

INTRODUCTION

For many decades, medication of an acute disease or a chronic illness has been accomplished by delivering drugs to the patients via various pharmaceutical dosage forms like tablets, capsules, pills, creams, ointments, liquids, aerosols, injectables and suppositories as carriers. To achieve and then to maintain the concentration of drug administered within the therapeutically effective range needed for medication, it is often necessary to take this type of drug delivery systems several times in a day. This results in a fluctuated drug level and consequently undesirable toxicity and poor efficiency. To minimize

this fluctuation, novel drug delivery systems have been developed, which include niosomes, liposomes, nanoparticles, microspheres microemulsions and magnetic microcapsules.

At present there is no specific drug delivery system which achieves the site specific delivery with controlled release kinetics of drug in predictable manner. Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes etc. Among different carriers liposomes and niosomes are well documented drug delivery. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with nontarget tissue.

Niosomes are the vesicles which are formed by hydrating mixture of cholesterol and non-ionic surfactants. These are formed by self assembly of non-ionic surfactants in aqueous media as spherical, unilamellar, multilamellar system and polyhedral structures in addition to inverse structures which appear only in nonaqueous solvent. Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs.

Niosome can enhance bioavailability of encapsulated drug and provide therapeutic activity in a controlled manner for a prolonged period of time. Niosome basically made of Non-ionic surfactants which provide advantages over the phospholipids because they are more economical and are chemically more stable as they are not easily hydrolysed or oxidized during storage.

Niosomes are microscopic lamellar structures of the size range between 10 to 1000 nm. The niosome consists of non-immunogenic, biodegradable and biocompatible surfactants. Niosomes are better than liposomes and its higher chemical stability of surfactants than phospholipids which are easily hydrolyzed due to the ester bond and cost effective.

The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic response may offer several advantages are-

- 1) Higher patient compliance in comparison with oily dosage forms.
- 2) The vesicles may act as a depot, releasing the drug in a controlled manner.
- 3) Accommodate drug molecules with a wide range of solubilities .

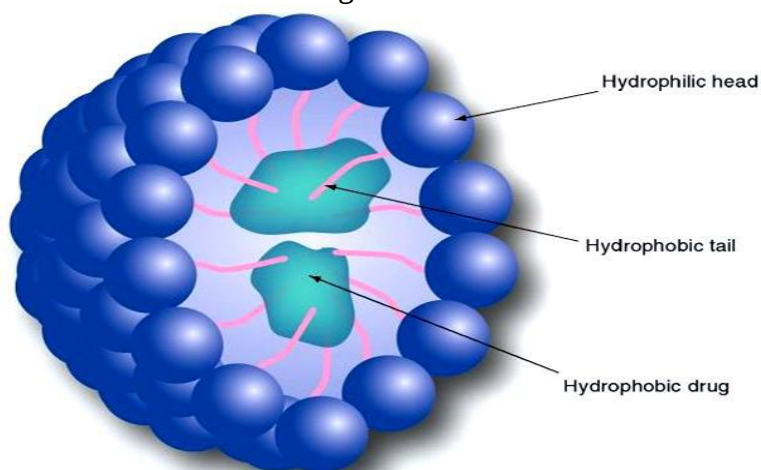


Fig. 1: Structure of Niosome.

Difference in the niosomal and liposomal system is that niosomal bilayer is formed by non-ionic surfactant where as liposomal bilayer made up of phospholipids. Niosomes are formed by the self assembly of non-ionic surfactants in aqueous media as spherical, unilamellar, bilayered, multilamellar system and polyhedral structures depending on the method used to prepare and the inverse structure in case of non-

aqueous solvent. The orientation of the surfactant in niosome in hydrophilic ends exposed outwards while hydrophobic ends face each other forming bilayer of the surfactant. The size of the niosomes ranges between 10 to 1000nm. Addition of cholesterol and a small quantity of anionic surfactant for instance dicetyl phosphate stabilizes the niosomal vesicles formed by the non-ionic surfactant. Niosomes are suggested to be better than liposomes because of the higher chemical stability of surfactants than phospholipids which are easily hydrolyzed due to the ester bond and cost effective Niosomes illustrate a promising drug delivery. Various methods of administration of niosomal formulation include intramuscular, intravenous, peroral and transdermal.

COMPOSITION OF NIOSOMES

Two components use in niosome preparation are

- Cholesterol
- Non-ionic surfactants

A. Cholesterol is a steroid derivative, which is used to provide rigidity and proper shape, conformation to niosome form.

B. Non-ionic Surfactants are generally used for the preparation of niosomes.

Examples: a. Tweens (20, 40, 60, 80)

b. Spans (Span 60, 40, 20, 85, 80)

c. Brij (Brij 30, 35, 52, 58, 72, 76).

DIFFERENT TYPES OF NON-IONIC SURFACTANTS

Table 1: Different Types of Non-Ionic Surfactants

Type of Non-Ionic Surfactant	Examples
Fatty alcohol	Cetyl alcohol, stearyl alcohol, cetostearylalcohol, oleyl alcohol
Ethers	Brij, Decyl glucoside, Lauryl glucoside, Octyl glucoside, Triton X-100, Nonoxynol-9
Esters	Glyceryl laurate, Polysorbates, Spans
Block copolymers	Poloxamers

TYPES OF NIOSOME

The various types of niosomes are described below:

- i) Multi lamellar vesicles (MLV),
- ii) Large unilamellar vesicles (LUV),
- iii) Small unilamellar vesicles (SUV).

1. Multi Lamellar Vesicles (MLV)

These vesicles consists of a number of bilayer surrounding the aqueous lipid compartment separately (approximate size of these vesicles is 0.5-10 μm diameter). Multilamellar vesicles are the most widely used niosomes.

2. Large Unilamellar Vesicles (LUV)

Large volumes of bioactive materials can be entrapped in these type of vesicles. Niosomes of this type have a high aqueous or lipid compartment ratio.

3. Small Unilamellar Vesicles (SUV)

This small unilamellar vesicles are mostly prepared from multi lamellar vesicles by sonication method.[6]

ADVANTAGES OF NOISOME

- a) Since the structure of the niosome offers place to accommodate hydrophilic, lipophilic as well as amphiphilic drug moieties, they can be used for a variety of drugs.
- b) Niosomes exhibit flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to the desired situation.
- c) They improve the therapeutic performance of the drug by protecting it from the biological environment and restricting effects to target cells, thereby reducing the clearance of the drug.
- d) Niosomes can act as a depot to release the drug slowly and offer a controlled release.
- e) They can increase the oral bioavailability of poorly soluble drugs.
- f) They are osmotically active and stable.
- g) They increase the stability of the entrapped drug.
- h) They can enhance the skin penetration of drug.
- i) They can be made to reach the site of action by oral, parenteral as well as topical routes.
- j) The surfactants are biodegradable, biocompatible, and non immunogenic, non-toxic.
- k) Handling and storage of surfactants do not require any special conditions.
- l) The vesicle suspension being water based offers greater patient compliance over oily dosage forms.
- m) They can protect the active moiety from biological circulation.

DISADVANTAGES OF NIOSOMES

1. Physical instability
2. Aggregation
3. Fusion
4. Leaking of entrapped drug
5. Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.

COMPARISON BETWEEN NIOSOMES AND LIPOSOMES

Table 2: Comparison between Niosomes and Liposomes²³⁻²⁷

LIPOSOMES	Noisome
More Expensive	Less Expensive
Require special methods for storage and handling of the final formulation.	No special methods require for such formulations.
Phospholipids may be neutral and charged.	Non-ionic surfactant is uncharged.

Niosomes Vs Liposomes

1. Niosomes are now widely studied as an alternative to liposomes, which exhibit certain disadvantages such as –they are expensive, their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they require special storage and handling and purity of natural phospholipids is variable.
2. Differences in characteristics exist between liposomes and niosomes, especially since niosomes are prepared from uncharged single-chain surfactant and cholesterol whereas liposomes are prepared from double-chain phospholipids (neutral or charged). Niosomes behave in-vivo like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability. Encapsulation of various anti neoplastic agents in these carrier vesicles has been shown to decrease drug induced toxic side effects, while maintaining, or in some instances, increasing the anti-tumour efficacy. Such vesicular drug carrier systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug. They can be expected to target the drug to its desired site of action and/or to control its release.
3. As with liposomes, the properties of niosomes depends both on the composition of the bilayer and on method of their production. The intercalation of cholesterol in the bilayers decreases the entrapment volume

during formulation and thus entrapment efficiency. As the concentration of cholesterol increases, entrapment efficiency decreases.

4. The entrapment efficiency increases with increase in the concentration and lipophilicity of surfactant. It was also observed that as HLB value of surfactant decreased, the mean size was reduced. Chandraprakash et al made Methotrexate loaded non-ionic surfactant vesicles using lipophilic surfactants like Span 40, Span 60 and Span 80 and found that Span 60 (HLB = 4.7) gave highest percent entrapment while Span 85 (HLB = 9.8) gave least entrapment.

METHODS OF PREPARATION

A. Thin film hydration technique

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar niosomes.

B. Micro fluidization

Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a greater uniformity, smaller size and better reproducibility of niosomes formed.

C. Reverse Phase Evaporation Technique (REV)

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes.

D. Ether injection method

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used, the diameter of the vesicle range from 50 to 1000nm.

E. Trans membrane pH gradient (inside acidic) Drug Uptake Process (remote Loading)

Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated with citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to give niosomes.

F. The "Bubble" Method

It is novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.

G. Sonication

A typical method of the vesicles is by sonication of solution as described by Cable. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes.

H. Formation of niosomes from proniosomes

Another method of producing niosomes is to coat a water-soluble carrier such as sorbitol with surfactant. The result of the coating process is a dry formulation. In which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed "Proniosomes". The niosomes are recognized by the addition of aqueous phase at $T > T_m$ and brief agitation. T = Temperature. T_m = mean phase transition temperature. Blazek-Walsh A.I. *et al.* [18] have reported the formulation of niosomes from maltodextrin based proniosomes. This provides rapid reconstitution of niosomes with minimal residual carrier. Slurry of maltodextrin and surfactant was dried to form a free flowing powder, which could be rehydrated by addition of warm water.

Carrier + surfactant = proniosomes,

Proniosomes + water = niosomes.

I. Multiple Membrane Extrusion Method -Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform forms thin film by rotary evaporator. The film hydrates with aqueous drug polycarbonate membranes. Solution and resultant suspension extrude through polycarbonate membrane and placed in series for up to 8 passages. It is a good method for niosome size control.

J. Emulsion Method: This is a simple method to form niosome in which oil in water (o/w) emulsion is prepared from an organic solution of surfactant, cholesterol, and an aqueous solution of the drug. Finally, the organic solvent is evaporated leaving niosomes dispersed in the aqueous phase.

K. Heating Method: This method is in one-step, scalable and non-toxic and also based on the patent procedure. A suitable aqueous medium such as buffer distilled water, etc. in which mixtures of non-ionic surfactants, cholesterol and/or charge inducing molecules are added in the presence of the polyol like as glycerol. The mixture is heated with (at low shear forces) until the vesicles were form.

L. Modified Lipid Injection Method: This method does not require expensive organic phase. Mixture of lipids and surfactant is first melted and then injected into a highly agitate heated aqueous phase contains the dissolved drug. Drug dissolves in molten lipid and the mixture will be injected into agitate, heat aqueous phase containing surfactant.

FACTORS INFLUENCING NIOSOMAL FORMULATION

1. Nature of Surfactant: Increase in the HLB value of surfactants leads to the increase in the mean size of niosomes due to the decrease in surface free energy with an increase in the surfactant hydrophobicity. The bilayers of the niosomes can exist either as a liquid state or in a gel state. It depends upon the temperature, type of surfactant and cholesterol. Alkyl chains are well ordered in the gel state, whereas disordered in the liquid state. Entrapment efficiency is affected by the gel, liquid phase transition temperature (TC) of the surfactant.

Eg: span 60 with higher TC exhibits better entrapment.

The HLB value of surfactants ranging between 14 and 17 are not suitable for niosomal preparations. Decrease in the HLB value of surfactants from 8.6 to 1.7 decreases the entrapment efficiency and highest entrapment efficiency is found with the HLB value of 8.6.

2. Nature of Encapsulated Drug: The charge and the rigidity of the niosomal bilayer are greatly influenced by physical chemical properties of the encapsulated drug. Entrapment of drug occurs by interacting with the surfactant head groups leading to the increasing charge and creates mutual repulsion of the surfactant bilayer and thus increases the vesicle size. The HLB of drug influences the degree of entrapment.

3. Hydration Temperature: The size and shape of the niosome are affected by the temperature of hydration. Hydration temperature should be above the gel, liquid phase transition temperature. Change in temperature affects the assembly of surfactants into vesicles and vesicle shape modification. Hydration time and volume of hydration medium also accounts for the modification. Improper selection of the hydration temperature, time and hydration medium volume produces fragile niosomes / drug leakage problems may arise.

4. Cholesterol Content: Incorporation of cholesterol increases the entrapment efficiency and hydrodynamic diameter of niosomes. Cholesterol acts in two ways:

- ☐ Increases the chain order of liquid state bilayers.
- ☐ Decreases the chain order of gel state bilayers.

An increase in the cholesterol concentration causes an increase in the rigidity of the bilayers and decrease in the release rate of encapsulated material.

5. Charge: Presences of charge leads to an increase in inter lamellar distance between successive bilayers in multi lamellar vesicle structure and greater overall entrapped volume.

6. Resistance to Osmotic Stress: Addition of hypertonic solution causes reduction in vesicle diameter. In hypotonic solution, inhibition of eluting fluid from vesicles results in the slow release initially followed by the faster release due to the mechanical loosening of vesicle structure under osmotic stress.

SEPARATION OF UNENTRAPPED DRUG⁻⁴⁸⁻⁴⁹

The removal of untrapped solute from the vesicles can be accomplished by various techniques, which include

1. Dialysis

The aqueous niosomal dispersion is dialyzed in a dialysis tubing against phosphate buffer or normal saline or glucose solution.

2. Gel Filtration

The untrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with

3. Centrifugation

The niosomal suspension is centrifuged and the supernatant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from untrapped drug.

METHOD FOR EVALUATION OF NIOSOMES

Table 3: Method for Evaluation of Niosomes

Evaluation Parameters	Method
Morphology	SEM, TEM, freeze fracture technique
Size distribution, polydispersity index	Dynamic light scattering particle size analyzer
Viscosity	Ostwald viscometer
Membrane thickness	X-ray scattering analysis
Thermal analysis	DSC
Turbidity	UV-visible diode array spectrophotometer
Entrapment efficacy	Centrifugation, dialysis, gel chromatography
Invitro release study	Dialysis membrane
Permeation study	Franz diffusion cell

1. Size and Shape: Various methods is used for the determination of mean diameter like as laser light scattering method besides it also determines by electron microscopy, molecular sieve chromatography, photon correlation microscopy, optical microscopy.

2. Scanning Electron Microscopy: The niosomes were observed under a scanning electron microscope (SEM) (JSM 6100 JEOL, Tokyo, Japan). They were mounted directly onto the SEM sample stub using double sided sticking tape and coated with gold film of thickness of 200 nm under reduced pressure of 0.001 mmHg. Photographs were taken at suitable magnification.

3. Number of lamellae

It is determined by using NMR spectroscopy, small angle X-ray scattering and electron microscopy.

4. In-vitro Release: In-vitro release rate study carried out by the use of

1. Dialysis Tubing,
2. Reverse dialysis and
3. Franz diffusion cell.

a. Dialysis Tubing: A dialysis sac is washed with distilled water. The prepared vesicle suspension is pipetted into a bag made up of the tubing dialysis and after that the bag is sealed. Then the bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°C. At various time intervals, the buffer is an analysis of the drug content of an appropriate assay method.

b. Reverse Dialysis: A number of small dialysis as containing 1ml of dissolution medium is placed in proniosomes. The proniosomes are then displaced into the dissolution medium. The direct dilution of the proniosomes is possible with this method and the rapid release cannot be quantified by using this method.

c. Franz Diffusion Cell: The in vitro diffusion studies can be performed by using Franz diffusion cell. Proniosomes is placed in the donor chamber of a Franz diffusion cell fitted with cellophane membrane. The proniosomes is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals and analyze for drug content using suitable method such as U.V spectroscopy, HPLC, etc. the maintenance of sink condition is essential.

5. Vesicle diameter

Niosomes diameter can be determined using light microscopy, photon correlation microscopy and freeze fracture electron microscopy. Freeze thawing (keeping vesicles suspension at -20°C for 24 hrs and then heating to ambient temperature) of niosomes increases the vesicle diameter, which might be attributed to fusion of vesicles during the cycle.

6. Membrane rigidity

Membrane rigidity can be measured by means of mobility of fluorescence probe as function of temperature.

7. Bilayer formation

Assembly of non-ionic surfactants to form bilayer vesicle is characterized by X-cross formation under light polarization microscopy.

8. Stability Study: Niosomal formulations are subject to stability studies by storing at 4°C, 25°C and 37°C in thermostatic oven for the period of three months. After one month, drug content of all the formulations are checked by entrapping efficiency parameter.

NATURE OF DRUG AND ITS EFFECT ON STABILITY

Table 4: Nature of drug and its effect on stability

Nature of the Drug	Leakage from the Vesicles	Stability
Hydrophobic drug	Decreases	Increases
Hydrophobic drug	Increases	Decreases
Amphiphilic drug	Decreases	-
Macromolecules	Decreases	Increases

Table 5: List of Drugs formulated as Niosome-

Routes of administration	Examples of drug
Intravenous route	Doxorubicin, Methotrexate, Sodium stibogluconate, Iopromide, Vincristine, Diclofenac sodium, Flurobiprofen, Centchronam, Indomethacin, Colchicine, Rifampicin, Tretinoin, Transferrin and Glucose ligands, Zidovudine, Insulin, Cisplatin, Amarogentin, Daunorubicin, Amphotericin B, 5-Fluorouracil, Camptothecin, Adriamycin, Cytarabine Hydrochloride
Peroral route	DNA vaccines, Proteins, Peptides, Ergot Alkaloids, Ciprofloxacin, Norfloxacin, Insulin
Transdermal routes	Flburiprofen, Piroxicim, Estradiol, Levonorgestrol, Nimesulide, Dithranol, Ketoconazole, Enoxacin, Ketorolac
Ocular route	Timolol Maleate, Cyclopentolate
Nasal route	Sumatriptan, Influenza Viral Vaccine
Inhalation	A11-trans retinoic acids

VARIOUS AGENTS ENCAPSULATED IN NIOSOMES AND THE CORRESPONDING RESULTS

Estradiol- Enhanced in vitro skin permeation of pronisome formulations.

Iopromide- Targeting of iopromide entrapped in MLV to the Kidney.

Flurbi profen- Enhanced bio-availability and anti-inflammatory activity of niosome encapsulated formulations as compared to conventional ointment base.

Timolol maleate- Sustained activity on ocular administration

Cytarabine Hydrochloride- Niosomal encapsulation provides sustained release delivery.

Rifampicin- Prolonged drug release

Cisplatin- Significant antimetastatic activity

Cytosine arabinoside- Effective release in acid environment

Tretinoin- Span 20 and Tween 80, Span 60 and Tween 80 combination gives good entrapment

Daunorubicin Hydrochloride- Improved therapeutic efficacy

Colchicine - Sustain release & reduced toxic side effects

Insulin - 1.Sustained release after oral dosage form

2. Enhancing effect on vaginal delivery of insulin

3. Improved stability against proteolytic enzyme

Finasteride- Enhance drug concentration by topical application

Hydroxycamphothecin- Enhanced stability and antitumor activity.

Acetazolamide - Prolonged effect and decrease in Intraocular pressure

Clotrimazole- Sustain and controlled release of clotrimazole for local vaginal therapy

Timolol maleate- Improved pharmacodynamics

Tetanus Toxoide- Mannosylated niosomes were found to be useful oral vaccine delivery carrier.

Propyl thiouracil- Control the release of propyl thiouracil.

Table 6:-Marketed Formulations of Niosome

S. No.	Brand	Name of the Product
---------------	--------------	----------------------------

1.	Lancome	Foundation & Complexion Flash Retouch Brush On Concealer
2.	Britney Spears- Curious	Curious Coffret: Edp Spray 100ml+ Dualended Parfum & Pink Lipgloss+ Body Souffle 100 ml
3.	Loris Azzaro – Chrome	Chrome Eau De Toilette Spray 200ml
4.	Helena Rubinstein - HR - Golden Beauty - Body Care	Golden Beauty After Sun Soothing Moisturizer 150ml
5.	Givenchy - Amarige	Amarige Eau De Toilette Spray 100ml
6.	Estee Lauder - Beyond Paradise	Beyond Paradise After Shave Lotion 100ml
7.	Orlane - Lipcolor & Lipstick	Lip Gloss
8.	Liz Claiborne – Realities	R e a l i t i e s Shower Gel 200ml
9.	White Shoulders	White Shoulders Eau De Cologne Spray 130ml
10.	Jean Paul Gaultier - Le Classique	Le Classique Eau De Toilette Spray 100ml
11.	Hugo Boss - Boss Soul	Boss Soul After Shave 90ml
12.	Lancaster - Suractif - Night Care	Suractif Non Stop Lifting Advanced Night Cream 50ml
13.	Givenchy - Blanc Parfait - Day Care	Blanc Parfait W4-L Universal Brightening Spots Corrector SPF 45 1.6ml

APPLICATIONS

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Few of their therapeutic applications are as follows:

1. Targeting of bioactive agents
 - a) To reticulo-endothelial system (RES)
 - b) To organs other than reticulo-endothelial system (RES)
2. Delivery of peptide drugs
3. Niosome as a carrier for Haemoglobin
4. Transdermal delivery of drugs by Niosome
5. Diagnostic imaging with niosomes
6. Ophthalmic drug delivery
7. Localized Drug Action
8. Hormones
9. Muscle Relaxants
10. Anaesthetics
11. Anti-Diabetic
12. Contraceptive.

MECHANISM OF TRANSDERMAL DRUG DELIVERY THROUGH NIOSOMES

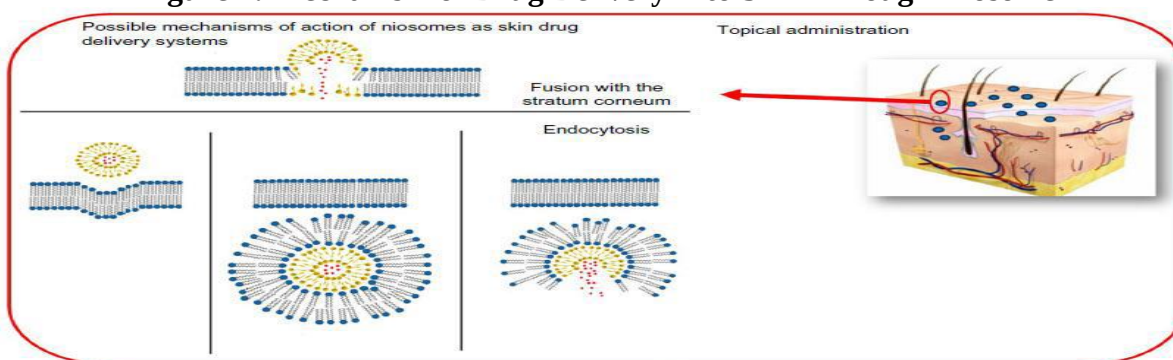
Transdermal delivery indicates the delivery of drugs through skin. Stratum corneum is the most impermeable barrier of the skin therefore for efficient drug delivery the formulation should be able to pass through this barrier.

□ There is no single mechanism that can completely explain the ability of niosomes to increase drug transfer through the skin and several mechanisms have been proposed which are as follows: Niosomes diffuse through the layer of stratum corneum after which the lipophilic drug crosses the stratum corneum through fusion, aggregation and adhesion. Then the niosomes cause the cells of the stratum corneum to be loosened thereby increasing the permeation of drugs. This permeation is enhanced by non-ionic surfactant which leads to improved drug permeation through skin. Niosomes adsorb on to cell surface with little or no internalization of either aqueous or lipid components, it may take place because of two reasons, either as a result of attracting physical forces or as a result of binding by specific receptors to ligands on the vesicle membrane and then transfer of drug directly from vesicles to the skin.

□ Niosomes may fuse with the cell membrane, which leads to complete mixing of the niosomal contents with the cytoplasm.

□ Finally, by the process of endocytosis, niosomes may be engulfed by the cell thus releasing the entrapped drug into the medium.⁷⁰⁻⁷¹

Figure 2: Mechanism of Drug Delivery Into Skin Through Niosome



CONCLUSION

The vesicular systems have been gaining a lot of interest of various researchers and scholars, because of their advantages of sustained and controlled release action, stability and versatility as a drug carrier. These carrier systems have immense scope in future, especially in the area of transdermal drug delivery. Niosomes are considered to be better candidates for drug delivery when compared to liposomes due to various factors like cost and stability. These advantages over the liposomes make it a better targeting agent. The usefulness of niosomes in the delivery of proteins and biologicals can be unsubstantiated with a wide scope in encapsulating toxic drugs such as anticancer drugs and anti-viral drugs. Drug delivery potential of niosome can be enhanced by using novel concepts like proniosomes, disomes and aspasome. Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant but they are at initial stage and thus these areas need further exploration and research so as to bring out commercially available niosomal preparation. Various routes of application can be possible using niosomes like targeting, ophthalmic, topical, parenteral, and oral.

REFERENCES:

- [1]. Chandu VP, Arunachalam A, Jeganath S, Yamini K, Tharangini K, Chaitanya G. Niosomes: A novel drug delivery system. *Int J of Novel Trends in Pharm Sci*, 2012; 2: 25-31.
- [2]. Khandare JN, Madhavi G, Tamhankar BM. Niosomes novel drug delivery system. *The Eastern*

- Pharmacist, 1994; 37: 61-64.
- [3]. Mujeeb SA, Krishna SA. Niosomes: A vesicular system for drug targeting. J Pharm and Bio Sci, 2015; 3: 24-31.
- [4]. Rekharao, Nanda S. Preparation and characterization techniques in niosomal vesicular systems. A Review J Pharma and Bio Sci, 2011; 5: 1-7.
- [5]. Singh SK, Rajera R, Nagpal K, Mishra DN. Niosomes: A controlled and novel drug delivery system. Bio Pharm Bull, 2011; 34: 945-953.
- [6]. Akhilesh D, Hazel G, Kamath J.V. Proniosomes –A Propitious Provesicular Drug Carrier. International Journal of Pharmacy and Pharmaceutical Science Research, 2011; 1: 98-103.
- [7]. Revathy BM, Lakshmi VS, Aiswarya MU, Keerthana R, Sreeja C.N. Porphysomes-A paradigm shift in targeted drug delivery. Int J App Pharma, 2018; 10: 1-6.
- [8]. Keshav J. Niosomes as a potential carrier system: A review. Int J Pharm Chem and Bio Sci, 2015; 5: 947-959.
- [9]. Rogerson A, Cummings J, Willmott N. The distribution of doxorubicin in mice following administration in niosomes. J Pharm Pharmacol, 1988; 40: 337-342.
- [10]. Yoshioka T, Stermberg B, Florence AT. Preparation and properties of vesicles (niosomes) of sobitan monoesters (Span 20, 40, 60, and 80) and a sorbitan triester (Span 85). Int J Pharm 1994; 105: 1-6.
- [11]. Srinivas S, Kumar AY, Hemanth A, Anitha M. Preparation and evaluation of niosomes containing aceclofenac. Dig J Nanomater Bios, 2010; 5: 249-254.
- [12]. Pardakhty A, Varshosaz J, Rouholamini A. In vitro study of polyoxyethylene alkyl ether niosomes for delivery of insulin. Int J Pharm, 2007; 328: 130-141.
- [13]. Ali N, Harikumar SL, Kaur A. Niosomes: An excellent tool for drug delivery. IJRPC, 2012; 2: 479-486.
- [14]. Girigoswami A, Das S, De S. Fluorescence and dynamic light scattering studies of niosomes membrane mimetic systems. Spectrochimica Acta, Part A, 2006; 64: 859–866.
- [15]. Cook EJ, Lagace AP. Apparatus for forming emulsions. US Patent 4254553, 1985.
- [16]. Kaur IP, Garg A, Singla AK. Vesicular systems in ocular drug delivery: an overview. Int J Pharm, 2004; 269: 1-14.
- [17]. Carafa M, Santucci E, Lucania G. Lidocaine-loaded non-ionic surfactant vesicles: characterization and in vitro permeation studies. Int J Pharm, 2002; 231: 21–32.
- [18]. Sudhakar CK, Upadhyay N, Jain S, Charyulu RN. Ethosomes as non-invasive loom for transdermal drug delivery in: Sebastian M, Ninan N, Haghi AK. editors Nanomedicine and Drug Delivery San Diego. Apple Academic Press, 2012; 1: 1-16.
- [19]. Mayer LD, Bally MB, Hope MJ, Cullis PR. Biochem Biophys Acta, 1985; 816: 294-302.
- [20]. Saeid M, Afra H. Nano-niosomes as nanoscale drug delivery system. Journal of Controlled Release, 2014; 185: 22-36.
- [21]. Verma S, Singh SK, Syan N, Mathur P, Valecha V. Nanoparticle vesicular systems: a versatile tool for drug delivery. J Chem Pharm Res, 2010; 2: 496-509.
- [22]. Alam M, Zubair S, Farazuddin M, Malik A, Mohammad O. Development, characterization and efficacy of niosomal diallyl disulfide in treatment of disseminated murine candidiasis.

- Nanomedicine, 2013; 9: 247-256.
- [23]. Shilpa, Srinivasan BP, Chauhan M. Niosomes as vesicular carriers for delivery of proteins and biologicals. *International Journal of Drug Delivery*, 2011; 3: 14-24.
- [24]. Uchegbu FI, VP. Non-ionic surfactant based vesicles (niosomes) in drug delivery. *Int J Pharm*, 1998; 172: 33-70.
- [25]. Chauhan S, Luorence MJ. The preparation of polyoxyethylene containing non-ionic surfactant vesicles. *J Pharm Pharmacol*, 1989; 41: 1-6.
- [26]. Sankhyan A, Pawar P. Recent Trends in Niosome as Vesicular Drug Delivery System. *Journal of Applied Pharmaceutical Science*, 2012; 2: 20-32.
- [27]. Raja Naresh RA, Chandrashekhar G, Pillai GK, Udupa N. Anti-inflammatory activity of niosome encapsulated diclofenac sodium with Tween-85 in arthritic rats. *Ind J Pharmacol*, 1994; 26: 46-48.
- [28]. Shilpa, Srinivasan BP, Chauhan M. Niosomes as vesicular carriers for delivery of proteins and biological. *Int J Drug Delivery*, 2011; 3: 14-24.
- [29]. Uchegbu FI, VP. Non-ionic surfactant based vesicles (niosomes) in drug delivery. *Int J Pharm*, 1998; 172: 33-70.
- [30]. Gibaldi M, Perrier D. *Pharmacokinetics*. 2nd edi. Marcel Dekker: New York; 1982; 127-134.
- [31]. Hao Y, Zhao F, Li N, Yang Y, Li K. Studies on a high encapsulation of colchicines by a niosome system. *Int J Pharm*, 2002; 244: 73-80.
- [32]. Uchegbu IF, Vyas SP. Non-ionic surfactant based vesicles (niosomes) in drug delivery. *Int J Pharm*, 1998; 172 :33-70.
- [33]. Pawar SD, Pawar RG, Kodag PP, Waghmare AS. Niosome: An unique drug delivery system. *Int J Bio Pharmacy and Allied Sci*, 2012; 3: 409-412.
- [34]. Sudhamani T, Priyadarisini N, Radhakrishnan M. Proniosomes A promising drug carrier. *Int J Pharm Tech Research*, 2010; 2: 14461454.
- [35]. Schreier H. Liposomes and niosomes as topical drug carriers: dermal and transdermal delivery. *J Controlled Release*, 1985; 30: 863-868.
- [36]. Negi P et al. Niosome-based hydrogel of resveratrol for topical applications: An effective therapy for pain related disorders. *Biomedicine & Pharmacotherapy*, 2017; 88: 480–487.
- [37]. Negi P, Singh B, Sharma G. Biocompatible lidocaine and prilocaine loaded Nanoemulsion system for enhanced percutaneous absorption: QbD-based optimization, Ex vivo and In vivo evaluation. *J Microencapsulation*, 2015; 1-13.
- [38]. Hunter CA, Dolan TF, Coombs GH, Baillie AJ. Vesicular systems (niosomes and liposomes) for delivery of sodium stibogluconate in experimental murine visceral leishmaniasis. *J Pharm Pharmacol*, 1988; 40: 161-65.
- [39]. Bairwa NK, Choudhary D. Proniosome: A review. *Asian J Biochem and Pharma Res*, 2011; 2: 690-694.
- [40]. Suzuki K, Soka K. The application of liposome's to cosmetics. *Cosmetic and Toiletries*, 1990; 105: 65-78.
- [41]. Niosomes, freeze-dried powder thereof and their use in treatment.
- [42]. Thakkar M, Brijesh S. Opportunities and Challenges for Niosomes as Drug Delivery Systems. *Current Drug Delivery*, 2016.

- [43]. Vadlamudi HC, Sevukarajan M, Niosomal Drug Delivery System-A Review, Indo American Journal of Pharmaceutical Research. 2012;2(9).
- [44]. Muzzalupo R, Tavano L, Niosomal Drug Delivery For Transdermal Targeting: Recent Advances, Research And Reports In Transdermal Drug Delivery, 2015:423-33.
- [45]. Rageeb MD, Usman, Ghuge PR, Jain BV, Niosomes: A Novel Trend of Drug Delivery, EJBPS, 2017; 4(7):436-442.
- [46]. Debnath A, Kumar A, Structural And Functional Significance of Niosome And Proniosome In Drug Delivery System, International Journal of Pharmacy And Engineering, 2015; 3(3):621-637.
- [47]. Sankhyan A, Pawar P, Recent Trends In Niosome as Vesicular Drug Delivery System, Journal of Applied Pharmaceutical Science 2012; 02(06):20-32.
- [48]. Rogerson A, The Distribution of Doxorubicin In Mice Following Administration In Niosomes, J Pharm, Pharmacol, 40(5):337-42.
- [49]. Mayer LD, Bally MB, Hope MJ, Cullis PR., Uptake of Antineoplastic Agents Into Large Unilamellar Vesicles In Response To A Membrane Potential, Biochem Biophys Acta. 1985; 816(2):294-302.
- [50]. Singh G, Dwivedi H, Saraf SK, Saraf SA, Niosomal Delivery of Isoniazid - Development And Characterization, Tropical J Pharm Res. April 2011; 10 (2):203-210.
- [51]. Lohumi A, Rawat S, Sarkar S, Sipai AB, Yadav MV, Review Article A Novel Drug Delivery System: Niosomes Review. J of Drug Delivery & Therapeutics 2012; 2(5):129-135.
- [52]. Madhav NVS, Saini A, Niosomes: A Novel Drug Delivery System, International Journal of Research in Pharmacy and Chemistry. 2011; 1(3):53. Safura Ayesha Mujeeb And Krishna Sailaja A, Niosomes: A Vesicular System For Drug Targeting, Journal Of Pharmaceutical And Biological Sciences, 2015; 3(1): 24-31.
- [53]. Chandu VP, Arunachalam A, Jeganath S, Yamini K, Tharangini K, Chaitanya G, Niosomes: A Novel Drug Delivery System, International Journal of Novel Trends in Pharmaceutical Sciences, 2012; 2(1).
- [54]. Gurjar P, Naik N, Chouksey S, Niosome: A Promising Pharmaceutical Drug Delivery, Int. J. Pharm Anal, 2(5):425-431.
- [55]. Shakya V, Bansal BK, Niosomes: A Novel Trend In Drug Delivery, International Journal of Research And Development In Pharmacy And Life Sciences, 2014, 3(4):1036-1041.
- [56]. Karim KM, Mandal AS, Biswas N, Guha A, Chatterjee S, Behera M, Kuotsu K, Niosome: A Future of Targeted Drug Delivery Systems Journal Of Advanced Pharmaceutical Technology & Research, 2010; 1(4).
- [57]. Jindal K, Niosomes as A Potential Carrier System: A Review, International Journal of Pharmaceutical, Chemical And Biological Sciences, 2015; 5(4):947-959.
- [58]. Sarker A, Shimu IJ, Alam SAA, Niosome: As Dermal Drug Delivery Tool, IOSR Journal of Pharmacy And Biological Sciences, 2015; 10(2):73-79.
- [59]. Nasir A, Harikumar SL, Kaur A, Niosomes: An Excellent Tool For Drug Delivery, IJRPC 2012; 2(2).
- [60]. Yoshida H, Lehr CM, Kok W, Junginger HE, Verhoef JC, Bouwstra JA, Niosomes for Oral Delivery of Peptide Drugs, Journal of Controlled Release, 1992; 21(1-3):145-153.

- [61]. Dwivedi C., Sahu R., Tiwari S., Satapathy T., Roy A. Role of liposome in novel drug delivery system. *Journal of Drug Delivery and Therapeutics*, 2014; 4(2):116-129.
- [62]. Biswal S, Murthy PN, Sahu J, Sahoo P, Amir F, Vesicles Of Non-Ionic Surfactants (Niosomes) And Drug Delivery Potential, *International Journal Of Pharmaceutical Sciences And Nanotechnology*, 2008; 1(1).
- [63]. Rastogi B., Nagaich U., Jain D. Development and characterization of non-ionic surfactant vesicles for ophthalmic drug delivery of diclofenac potassium. *Journal of Drug Delivery and Therapeutics*, 2014; 1-6.
- [64]. Hunter CA, Dolan TF, Coombs GH, Baillie AJ, Vesicular Systems (Niosomes And Liposomes) For Delivery of Sodium Stibogluconate In Experimental Murine Visceral Leishmaniasis, *J Pharm Pharmacol*. 1988; 40(3):161-165.
- [65]. Pola Chandu V, Arunachalam A, Jeganath S, Yamini K, Tharangini K, Chaitanya G, Niosomes: A Novel Drug Delivery System, *International Journal of Novel Trends In Pharmaceutical Sciences*, 2012; 2(1).
- [66]. Tangri P, Khurana S, Niosomes: Formulation and Evaluation, *International Journal Of Biopharmaceutics*. 2011; 2(1):47-53.
- [67]. Jaiswal P., Kesharwani S., Kesharwani R., Patel D. Ethosome: a new technology used as topical & transdermal delivery system. *Journal of Drug Delivery and Therapeutics*, 2016; 6(3):7-17
- [68]. Keservani RK, Sharma AK, Ayaz MD, Novel Drug Delivery System For The Vesicular Delivery of Drug By The Niosomes, *International Journal of Research in Controlled Release* 2011; 1(1):1-8.
- [69]. Rita Muzzalupo and Lorena Tavano. Niosomal drug delivery for transdermal targeting: recent advances. *Research and reports in transdermal drug delivery* 2015;(4):23-33.
- [70]. Prabha Singh, Huda Ansari, Shalan Dabre, Niosomes- A Novel Tool For Anti-Ageing Cosmeceuticals, Vol 6, Issue 10, 2016, P.No.-6691-670.